

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. *(withdrawn)*: A method for obtaining a prognosis for a subject having, or at risk of developing, an inflammatory condition, the method comprising determining a genotype of said subject which includes one or more polymorphic sites in the subject's protein C sequence; EPCR sequence or a combination thereof, wherein said genotype is indicative of an ability of the subject to recover from the inflammatory condition.

2. *(withdrawn)*: The method of claim 1, wherein the polymorphic site is

- (a) position 4732 of SEQ ID NO:1; or position 4054 of SEQ ID NO:2; or a polymorphic site in linkage disequilibrium thereto; or
- (b) a combination of Protein C and EPCR sequences, wherein said polymorphic sites are at two or more of positions selected from 4732 of SEQ ID NO:1; 4054 of SEQ ID NO:2; 2418 of SEQ ID NO:1; and a polymorphic site in linkage disequilibrium thereto.

3. CANCELED

4. *(withdrawn)*: The method of claim 2, wherein

- (a) the polymorphic site in linkage disequilibrium with position 4732 may be selected from positions 4813, 6379, 6762, 7779, 8058, 8915 and 12228 of SEQ ID NO: 1;
- (b) the polymorphic site in linkage disequilibrium with position 4054 may be selected from positions 2973, 3063, 3402, 4946, 5515 and 6196 of SEQ ID NO: 2;
- (c) the polymorphic site in linkage disequilibrium with position 2418 may be selected from positions 1386, 2583 and 3920 in SEQ ID NO: 1;
- (d) the polymorphic site in linkage disequilibrium with position 4732 may be selected from a combination of two polymorphic sites, which sites occur at any of the following combinations of positions in SEQ ID NO:1:

9198 and 5867;

9198 and 4800;

3220 and 5867; and

3220 and 4800;

and/or

- (e) the polymorphic site in linkage disequilibrium with position 2418 may be selected from a combination of two polymorphic sites, which sites occur at any of the following combinations of positions in SEQ ID NO:1:

5867 and 2405;

5867 and 4919;

5867 and 4956;

5867 and 6187;

5867 and 12109;

4800 and 2405;

4800 and 4919;

4800 and 4956;

4800 and 6187; and

4800 and 12109.

5 to 9: CANCELED

10. *(withdrawn)*: The method of claim 1, further comprising obtaining protein C sequence information or EPCR sequence information for the subject.
11. *(withdrawn)*: The method of claim 1, wherein the genotype is determined using a nucleic acid sample from the subject.
12. *(withdrawn)*: The method of claim 11, further comprising obtaining the nucleic acid sample from the subject.
13. *(withdrawn)*: The method of claim 1, wherein said genotype is determined using one or more of the following techniques:
- (a) restriction fragment length analysis;
 - (b) sequencing;
 - (c) hybridization;
 - (d) oligonucleotide ligation assay;
 - (e) ligation rolling circle amplification;
 - (f) 5' nuclease assay;
 - (g) polymerase proofreading methods;
 - (h) allele specific PCR; and
 - (i) reading sequence data.

14. *(withdrawn)*: The method of claim 1, wherein

- (a) the genotype of the subject is indicative of a decreased ability to recover from the inflammatory condition, or
- (b) the subject is critically ill and the genotype is indicative of a prognosis of severe cardiovascular or respiratory dysfunction.

15. CANCELED

16. *(withdrawn)*: The method of claim 14, wherein the genotype comprises

- (a) at least one of the following single polymorphic nucleotides or combinations of polymorphic nucleotides at the indicated positions of SEQ ID NO: 1:
 - 4732 C;
 - 4813 A;
 - 6379 G;
 - 6762 A;
 - 7779 C;
 - 8058 T;
 - 8915 T;
 - 12228 T;
 - 9198 C and 5867 A;
 - 9198 C and 4800 G;
 - 3220 A and 5867 A; and
 - 3220 A and 4800 G, or
 - 1386 T;
 - 2418 A;
 - 2583 A;
 - 3920 T;
 - 5867 A and 2405 T;
 - 5867 A and 4919 A;
 - 5867 A and 4956 T;
 - 5867 A and 6187 C;
 - 5867 A and 12109 T;
 - 4800 G and 2405 T;
 - 4800 G and 4919 A;
 - 4800 G and 4956 T;
 - 4800 G and 6187 C; and
 - 4800 G and 12109 T; and
- (b) at least one of the following EPCR polymorphic nucleotides at the indicated positions of SEQ ID NO: 2:
 - 6196 G;
 - 5515 T;
 - 4946 T;

4054 T;
3402 G;
3063 G; and
2973 C.

17. CANCELED

18. (*withdrawn*): The method of claim 16, wherein the genotype of the subject is indicative of an increased ability to recover from the inflammatory condition.

19. (*withdrawn*): The method of claim 18, wherein the subject is critically ill and the genotype is indicative of a prognosis of mild cardiovascular or respiratory dysfunction.

20. (*withdrawn*): The method of claim 14, wherein the genotype comprises

- (a) at least one of the following genotypes or genotype combinations within SEQ ID NO:1:
4732 T;
4813 G;
6379 A;
6762 G;
7779 -;
8058 C;
8915 G;
12228 C;
9198 A and 5867 G;
9198 A and 4800 C;
3220 G and 5867 G; and
3220 G and 4800 C,
or
1386 C;
2418 G;
2583 T;
3920 C;
5867 G and 2405 C;
5867 G and 4919 G;
5867 G and 4956 C;
5867 G and 6187 T;
5867 G and 12109 C;
4800 C and 2405 C;
4800 C and 4919 G;
4800 C and 4956 C;
4800 C and 6187 T; and
4800 C and 12109 C;
and

(b) at least one of the following genotypes within SEQ ID NO: 2:

6196 C;
5515 C;
4946 C;
4054 C;
3402 C;
3063 A; and
2973 T.

21 CANCELED

22. (*withdrawn*): The method of claim 1, wherein the inflammatory condition is selected from the group consisting of: sepsis, septicemia, pneumonia, septic shock, systemic inflammatory response syndrome (SIRS), Acute Respiratory Distress Syndrome (ARDS), acute lung injury, aspiration pneumonia, infection, pancreatitis, bacteremia, peritonitis, abdominal abscess, inflammation due to trauma, inflammation due to surgery, chronic inflammatory disease, ischemia, ischemia-reperfusion injury of an organ or tissue, tissue damage due to disease, tissue damage due to chemotherapy or radiotherapy, and reactions to ingested, inhaled, infused, injected, or delivered substances, glomerulonephritis, bowel infection, opportunistic infections, and for subjects undergoing major surgery or dialysis, subjects who are immunocompromised, subjects on immunosuppressive agents, subjects with HIV/AIDS, subjects with suspected endocarditis, subjects with fever, subjects with fever of unknown origin, subjects with cystic fibrosis, subjects with diabetes mellitus, subjects with chronic renal failure, subjects with bronchiectasis, subjects with chronic obstructive lung disease, chronic bronchitis, emphysema, or asthma, subjects with febrile neutropenia, subjects with meningitis, subjects with septic arthritis, subjects with urinary tract infection, subjects with necrotizing fasciitis, subjects with other suspected Group A streptococcus infection, subjects who have had a splenectomy, subjects with recurrent or suspected enterococcus infection, other medical and surgical conditions associated with increased risk of infection, Gram positive sepsis, Gram negative sepsis, culture negative sepsis, fungal sepsis, meningococemia, post-pump syndrome, cardiac stun syndrome, myocardial infarction, stroke, congestive heart failure, hepatitis, epiglottitis, E. coli 0157:H7, malaria, gas gangrene, toxic shock syndrome, pre-eclampsia, eclampsia, HELLP syndrome, mycobacterial tuberculosis, Pneumocystis carinii, pneumonia, Leishmaniasis, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, Dengue hemorrhagic fever, pelvic inflammatory disease, Legionella, Lyme disease, Influenza A, Epstein-Barr virus, encephalitis, inflammatory diseases and autoimmunity including Rheumatoid arthritis, osteoarthritis, progressive systemic sclerosis, systemic lupus erythematosus, inflammatory bowel disease, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, systemic vasculitis, Wegener's granulomatosis, transplants including heart, liver, lung kidney bone marrow, graft-versus-host disease, transplant rejection, sickle cell anemia, nephrotic syndrome, toxicity of agents such as OKT3, cytokine therapy, and cirrhosis.

23. (*withdrawn*): The method of claim 22, wherein the inflammatory condition is SIRS.

24 to 31 CANCELED

32. *(withdrawn)*: A method for selecting a group of subjects for determining the efficacy of a candidate drug known or suspected of being useful for the treatment of an inflammatory condition, the method comprising determining a genotype at one or more polymorphic sites in the protein C sequence or EPCR sequence for each subject, wherein said genotype is indicative of the subject's ability to recover from the inflammatory condition and sorting subjects based on their genotype.

33. *(withdrawn)*: The method of claim 32 further comprising, administering the candidate drug to the subjects or a subset of subjects and determining each subject's ability to recover from the inflammatory condition.

34. *(withdrawn)*: The method of claim 33, further comprising comparing subject response to the candidate drug based on genotype of the subject.

35. CANCELED

36. *(currently amended)*: A method of treating systemic inflammatory response syndrome (SIRS) an inflammatory condition in a human subject in need thereof, the method comprising:

- (a) selecting a human subject having a risk genotype for SIRSsaid inflammatory condition in his protein C sequence or EPCR sequence, which subject has one of more of the following wherein the risk-genotypes is located at a polymorphic site at one or more of the following positions:
 - (i) CC or CT at 4732 of SEQ ID NO:1;
 - (ii) TT or TC at 4054 of SEQ ID NO:2,
 - (iii) AA or AG at 2418 of SEQ ID NO:1, or
 - (iv) a genotype single polymorphic site in linkage disequilibrium (LD) with position 4732; 4054; and 2418, which single polymorphic site is found, respectively, at as follows:
 - (1) for sites in LD with position 4732 of SEQ ID NO:1: position AA or AG at 4813, GG or GA at 6379, AA or AG at 6762, CC or C- at 7779, TT or TC at 8058, TT or TG at 8915 or TT or TC at 12228 of SEQ ID NO:1;
 - (2) for sites in LD with position 4054 of SEQ ID NO:2: position CC or CT at 2973, GG or GA at 3063, GG or GC at 3402, TT or TC at 4946, TT or TC at 5515 or GG or GC at 6196 of SEQ ID NO:2; or

- (3) for sites in LD with position 2418 of SEQ ID NO:1: ~~position-TT or TC at 1386, AA or AT at 2583 or TT or TC at 3920~~ in SEQ ID NO:1; or
- (v) a combination of genotypes ~~two sites~~ in SEQ ID NO:1 which are in LD with position 4732 in SEQ ID NO:1 selected from the group of genotypes at positions consisting of:
- (1) CC or CA at 9198 and AA or AG at 5867;
 - (2) CC or CA at 9198 and GG or GC at 4800;
 - (3) AA or AG at 3220 and AA or AG at 5867; and
 - (4) AA or AG at 3220 and GG or GC of 4800;
- (vi) a combination of genotypes ~~two sites~~ in SEQ ID NO:1 which are in LD with position 2418 in SEQ ID NO:1, selected from the group of genotypes at positions consisting of:
- (1) AA or AG at 5867 and TT or TC at 2405;
 - (2) AA or AG at 5867 and AA or AG at 4919;
 - (3) AA or AG at 5867 and TT or TC at 4956;
 - (4) AA or AG at 5867 and CC or CT at 6187;
 - (5) AA or AG at 5867 and TT or TC at 12109;
 - (6) GG or GC at 4800 and TT or TC at 2405;
 - (7) GG or GC at 4800 and AA or AG at 4919;
 - (8) GG or GC at 4800 and TT or TC at 4956;
 - (9) GG or GC at 4800 and CC or CT at 6187; and
 - (10) GG or GC at 4800 and TT or TC at 12109, and

(b) administering to said human subject selected in (a) an activated protein C; ~~wherein the inflammatory condition is sepsis, septic shock or systemic inflammatory response syndrome (SIRS).~~

37 to 43: CANCELED

44. *(previously presented)*: The method at claim 36, further comprising determining the subject's APACHE II score as an assessment of subject risk.

45. *(previously presented)*: The method of claim 36, further comprising determining the number of organ system failures for the subject as an assessment of subject risk.

46. *(previously presented)*: The method of claim 44, wherein, an APACHE II score ≥ 25 is indicative of increased risk.

47. *(previously presented)*: The method of claim 45, wherein two or more organ system failures are indicative of increased subject risk.

48. to 59. CANCELED

60. *(currently amended)*: The method of ~~claim 36~~~~claim 58~~, wherein the genotype of the subject is indicative of an increased risk of poor outcome from the SIRS ~~inflammatory condition~~.

61. *(currently amended)*: The method of claim 60, wherein the subject who has an increased risk of poor outcome from SIRS ~~the inflammatory condition~~ is preferentially selected for administration of the activated protein C.

62 to 67. CANCELED

68. *(currently amended)*: The method of claim 36, wherein the activated protein C is drotrecogin ~~s drotrecogin~~ alpha activated.

69 to 87: CANCELED

88. *(previously presented)*: The method of claim 36, wherein the risk genotype is located at a polymorphic site at one or both positions 4732 of SEQ ID NO:1 and 4054 of SEQ ID NO:2.

89. CANCELED

90. *(new)*: A method of identifying a human subject at risk of death in whom treatment with activated protein C decreases said risk, the method comprising:

- (A) selecting human subjects having an APACHE II score of ≥ 25 as an indication of the subjects' risk of death; and
- (B) further selecting from the subjects selected in (a), those subjects who also have one or more of the following protein C or EPCR risk genotypes at one or more of the following indicated nucleotide positions:
 - (1) CC or CT at 4732 of SEQ ID NO:1,
 - (2) TT or TC at 4054 of SEQ ID NO:2,
 - (3) AA or AG at 2418 of SEQ ID NO:1,
 - (4) one or more of the following genotypes in SEQ ID NO:1 that is in LD with position 4732 in SEQ ID NO:1:
 - (a) AA or AG at 4813,
 - (b) GG or GA at 6379,

- (c) AA or AG at 6762,
 - (d) CC or C- at 7779,
 - (e) TT or TC at 8058,
 - (f) TT or TG at 8915, and
 - (g) TT or TC at 12228,
- (5) one or more at the following a genotypes in SEQ ID NO:2 that is in LD with position 4054 in SEQ ID NO:2:
- (a) CC or CT at 2973,
 - (b) GG or GA at 3063,
 - (c) GG or GC at 3402,
 - (d) TT or TC at 4946,
 - (e) TT or TC at 5515, and
 - (f) GG or GC at 6196,
- (6) one or more of the following genotypes in SEQ ID NO:1 that is in LD with position 2418 in SEQ ID NO:1:
- (a) TT or TC at 1386,
 - (b) AA or AT at 2583, and
 - (c) TT or TC at 3920,
- (7) one or more of the following combinations of genotypes in SEQ ID NO:1 that are in LD with position 4732 in SEQ ID NO:1:
- (a) CC or CA at 9198 and AA or AG at 5867;
 - (b) CC or CA at 9198 and GG or GC at 4800;
 - (c) AA or AG at 3220 and AA or AG at 5867; and
 - (d) AA or AG at 3220 and GG or GC at 4800; or
- (8) one or more of the following combinations of genotypes in SEQ ID NO:1 that are in LD with position 2418 in SEQ ID NO:1:
- (a) AA or AG at 5867 and TT or TC at 2405,
 - (b) AA or AG at 5867 and AA or AG at 4919,
 - (c) AA or AG at 5867 and TT or TC at 4956,
 - (d) AA or AG at 5867 and CC or CT at 6187,
 - (e) AA or AG at 5867 and TT or TC at 12109,
 - (f) GG or GC at 4800 and TT or TC at 2405,
 - (g) GG or GC at 4800 and AA or AG at 4919,
 - (h) GG or GC at 4800 and TT or TC at 4956,
 - (i) GG or GC at 4800 and CC or CT at 6187, and
 - (j) GG or GC at 4800 and TT or TC at 12109,

thereby identifying said subject.

91. (*new*): The method of claim 90, wherein the activated protein C is drotrecogin alfa activated.
92. (*new*): The method of claim 36, wherein the human subject has sepsis.
93. (*new*): The method of claim 36, wherein the human subject has septic shock.